Microbicides Research and Development: State of the Art

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Post-Graduate Course, Training in Research in Sexual Health, 9 March 05
Overview of Presentation

- The need for women-controlled methods
- What are microbicides?
- Mechanisms of action
- Microbicide pipeline
- Public health benefits
- Products in effectiveness trials
- Trial design issues
- Scientific challenges
- WHO Microbicide Project
Overview

• HIV/AIDS pandemic
  – Accounts for more deaths than other infectious disease
  – 40 million people currently infected world wide
  – about 6 out of every 10 new infections are in women
  – nearly 5,000 women are infected with HIV daily
  – 90% of them in developing countries

• HIV preventive strategies
  – Abstinence, monogamy, condom use, reduction in number of sexual partners
  – diagnosis and treatment of sexually transmitted diseases
Women and HIV

Increasingly Female

- 67% of African cases in 15-24 year olds
- In sub-Saharan Africa, 13 women for every 10 infected men
- In South Africa - 1 in 4 women infected by 22
- In India - in 2004, 22% of cases in housewives with single partner

Married, monogamous

Mother

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HIV interventions are often not feasible for many women

- Women with single partners can be exposed to HIV via their partners’ other sexual relationships
- Reduction of sex partners is not an option for commercial sex workers
- Many women do not have the power to insist on condom use
- Multiple sexual partners may be the only source of economic and social security
- Diagnosis and treatment of sexually transmitted infections are either unavailable or inadequate in many parts of the world, besides many infections in women are asymptomatic

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What is a microbicide?

- Any compound that can be applied into the vagina or rectum before sex to kill, neutralize, or block HIV and other sexually transmitted infections
- To date, no microbicide is available
  - they are under development and/or investigation
Other Microbicide Features

- Microbicides are inserted by women and may not require active negotiation with male partner
- Some are contraceptive, others are not contraceptive
- Potential protection against a range of STIs
- Could be used alone or together with a physical barrier (condoms, cervical barriers) as adjunct or fall-back
- Effective immediately after insertion and remains effective for several hours
- Potential effectiveness for post-coital and rectal use
- Could be made available over-the-counter at low cost

Courtesy: Janneke van de Wijgert

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How Microbicides Work (1)

- **Viral disruption/inactivation**

- **Prevention of other STDs**

- **physical barrier lubrication**

- **Maintenance of normal microflora and epithelial health**

*Courtesy: Zeda Rosenberg, PhD*
How Microbicides Work (2)

- Inhibition of HIV uptake by dendritic cells:
  - DC-SIGN mAbs
  - Mannan

- Inhibition of reverse transcriptase:
  - NRTIs - PMPA
  - NNRTIs - UC781, TMC 120, DABO, MIV 150

- Entry Inhibitors:
  - Polyanions
  - Coreceptor antagonists
  - Small molecule inhibitors
    - CD4 mAbs
    - BMS 806
    - T-20
    - Cyanovirin
    - Plant lectins

- Membrane Disruptive Agents:
  - C31G, SLS
  - Cyclodextrins

- Lumen
- Epithelium
- Stroma
Public Health Impact

• Research showed that offering more prevention choices results in more sex acts being protected and higher levels of condom use.

• Scientists at LSHTM calculated that 2.5 million infections could be averted over 3 years if a microbicide that is 60% effective were used by 20% of women in half of all sex acts that do not involve a condom. This would save society $2.7 billion in health care costs and $1 billion in productivity gains.
Product Selection Algorithm

Potential Microbicide

In Vitro anti-HIV Activity

High

Low

In Vitro Vaginal Toxicity

High

Low

In Vitro Genotoxicity

Positive

Negative

In Vivo Animal Vaginal Toxicity

High

Low

General Toxicology

Poor

Good

Animal Efficacy Studies (SIV/SHIV)

Laboratory strains
Clinical isolates/clades (R5)
Primary cells
Cervical/vaginal explants
Synergistic activity

Vaginal cell cytotoxicity
Lactobacilli
Pro-inflammatory potential

14-day Rabbit Vaginal Irritation Study

Safety Studies in Women

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Courtesy: Polly Harrison
The Pipeline by Mechanism of Action

- Replication Inhibitors (5)
- Entry & Fusion Inhibitors (20)
- Adsorption Inhibitors (11)
- Surfactants (6)
- Acid Buffers (3)
- Vaginal Defense Enhancers (7)
- Devices (3)
- Uncharacterized Mechanisms (6)
- Multiple Mechanisms (1)

Courtesy: Polly Harrison

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Scientific challenges
Basic science research (1)

• Cellular and molecular process at mucosal level not well understood → microenvironment
• Products with one mode of action → may have limited efficacy and potential for resistance
• products with uncharacterised mechanisms of action → cannot advance through the pipeline
• non-specific inhibition or blocking of receptor sites → potential toxicity
• combination products → which products?
• difficulties in formulation

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Scientific challenges
Basic science research (2)

• Pre-clinical assessment was initially based on assays for contraceptive and therapeutic products
• need to develop in vivo testing assays, ex vivo and animal models relevant to microbicides
• different labs use different assay systems, thus difficulties in comparing results
• animal models do not capture relevant features of sexual transmission in humans
  – interpretation of animal data is complicated
  – viral stocks lose mucosal infectivity over time
Scientific challenges

Ideal formulation

• Maintenance of vaginal PH
• Chemical and physical stability
• Activity throughout shelf life
• odorless
• Non-irritating to genital epithelium
• Non-disruptive to innate vaginal microflora
• rapid and sustained release of active ingredient
• retention of active ingredients over time
## Products in Clinical Research

<table>
<thead>
<tr>
<th>Phase 1</th>
<th>Phase 1/2</th>
<th>Phase 2</th>
<th>Phase 2/2B</th>
<th>Phase 3</th>
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</thead>
<tbody>
<tr>
<td>Acidform™/ Amphora™ + Diaphragm</td>
<td>Invisible Condom™</td>
<td>Human monoclonal antibodies (C2F5, C2G12, C4E10)</td>
<td>BufferGel™ PRO 2000 (0.5%)</td>
<td>Carraguard®</td>
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<td>Carraguard®</td>
<td>Praneem Polyherbal</td>
<td>PRO 2000 (0.5%) Tenofovir/ PMPA</td>
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<td>Cellulose sulfate</td>
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<td>Cellulose acetate phthalate</td>
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<td>Protected lactobacillus in combination w/ BZK</td>
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<td>PRO 2000 (0.5%, 2%)</td>
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<tr>
<td>Cellulose acetate phthalate 13%</td>
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<td>Tenofovir/ PMPA</td>
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<td>Savvy™/C-31G</td>
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<tr>
<td>Cellulose sulfate + Diaphragm</td>
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<td>Lactin-V capsule</td>
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<td>Lime Juice</td>
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<tr>
<td>Polystyrene sulfonate (PSS)</td>
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<tr>
<td>TMC-120 Gel</td>
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<tr>
<td>TMC-120 + Ring</td>
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<td>UC-781</td>
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<td>SPL7013</td>
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Courtesy: Polly Harrison
Phase III Clinical trials  Endpoints

• primary endpoint for all is HIV

• secondary endpoints:
  – BV (BufferGel™, PRO 2000)
  – chlamydia (BufferGel™, Cellulose sulfate, PRO 2000, Savvy™)
  – genital ulcer disease (BufferGel™, PRO 2000)
  – gonorrhea (BufferGel™, Cellulose sulfate, PRO 2000, Savvy™)
  – HSV-2 (BufferGel™, PRO 2000)
  – syphilis (BufferGel™, PRO 2000)
  – trichomoniasis (BufferGel™, PRO 2000)

• 3 are contraceptive:
  – BufferGel™, Cellulose sulfate, Savvy™

Courtesy: Polly Harrison
Clinical Trial Phases

- **Phase I**
  - Initial trials in human, involving a few subjects
  - To evaluate the safety/acceptability of the product

- **Phase II**
  - Expanded safety/acceptability
  - To determine appropriate dosage
  - Proof-of-concept
  - IIa: efficacy and short term safety
  - IIb: efficacy, side effects and clinical toxicity

- **Phase III**
  - To determine efficacy
  - Large trial involving hundreds or thousands of people
Phase IIB/III TRIALS

- CONRAD Trial (Cellulose sulfate)
- HPTN 035 Trial (BufferGel & PRO 2000)
- MDP 301 Trial (0.5% & 2% PRO 2000)
- Carraguard Trial (Carrageenum)
- SAVVY Trial (C31G)
CONRAD TRIAL

- Phase III trial, to start in late 2004
- Randomized, triple-blind, placebo-controlled
- Two arms (6% cellulose sulfate and placebo)
- Sample size-2,574 HIV-negative women
- Sites
  - Chennai, India (one more site)
  - Cotonou, Benin
  - Bobo Dioulasso, Burkina Faso
  - Durban, South Africa
  - Kampala, Uganda
HPTN 035 TRIAL

• Phase II and IIb safety and effectiveness study
• Randomized, four-arm (2 active products, 2 control arms)
• Active arms-BufferGel and PRO 2000
• Control arms (placebo and No-gel arm)
• Sample size 3100 HIV-negative women
  – 800 women in the phase II portion
• Sites
  – Pune (India), Blantyare and Lilogwe (Malawi), Chitungwiza and Harare (Zimbabwe), Durban (South Africa), Lusaka (Zambia), Moshi (Tanzania)
MDP 301 TRIAL

• To start in 2005
• Phase III trial
• Sponsorship: UK MRC, DfID, Indevus
• Active products: 0.5% and 2% PRO 2000/5 gel
• Sample size-11,920 HIV-negative women
• Current Sites
  – Primary health care facilities in Durban, Johannesburg and Mtubatuba (South Africa)
  – Primary health care facilities in Mazabuka (Zambia)
  – Nakambala sugar estate (Mazabuka, Zambia)
  – HIV sero-discordant couples (Masaka, Uganda)
• Future sites?
  – Sex workers in Yaounde, Cameroon
  – Big Bend sugar estate, Swaziland

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CARRAGUARD TRIAL

- Previously known as PC-515
- Phase III safety and effectiveness study
- Randomized, two-arms
- Products: Carraguard versus Methyl cellulose placebo
- Sample size 6,270 HIV-negative women
- Sites (all in South Africa)
  - Gugulethu (Cape Town)
  - Soshanguve (Pretoria)
  - Isipingo (Durban)
- Recruitment started in March 2004

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SAVVY TRIAL

• Known as C31G
• Sponsorship: FHI, Biosyn/Cellegy & USAID
• Two Phase III trials in West Africa (Ghana and Nigeria)
• Products (C31G versus placebo)
• Sample size 4,400 HIV-negative women
• Sites
  – Kumasi and Accra (Ghana)
  – Lagos and Ibadan (Nigeria)
• Completion expected in mid-2006
Phase III Trials and US FDA

- Two years ago, US FDA was consulted by the HPTN
- Initial advice: 2 phase III trials at 2-sided 0.05 significance
- Disadvantages:
  - Large sample sizes of 16,000 people
  - Very expensive (20m-80m US dollars)
  - If initial study is significant, unethical to conduct the other
- Revised FDA position:
  - Equivalent of one and half trials (12,000 people)
  - Choice of control arms

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Potential Mechanisms of effect of Microbicides and placebos

~ Antimicrobial effects
~ Physical Barrier effects
~ Lubrication effects
~ Other

*Design to Address Multiple Mechanisms*

Arms
- Active Microbicide
- Placebo Control
- Unblinded Control

Courtesy: Thomas Fleming, PhD

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Choice of Control Arm

• Randomization
  – Ensures balance of factors related to individual risk and to patterns of condom and product use
  – Cannot balance changes of behaviour once study group has been revealed

• Require good masking (or blinding)

• Placebo-controlled double-blind trial
  – Preferred whenever feasible
  – Gives unbiased estimate of product effectiveness
Rationale for a No-Product Arm

• “Placebo” may have some activity
  - potential for activity due to low pH; preservatives; dilution; physical barrier
• Provides a comparator that reflects the “real world” effectiveness of the products (i.e., versus no gel at all).
  - takes into account potential changes in behavior associated with use or non-use of a microbicide product.
  - Incidence among women in no-product arm
• Allows for possibility or performing analyses of the potential effects of the placebo gel on HIV transmission.
No-product Arm?

• Essential when no placebo product available
  – Cannot rely on randomization and blinding to balance behaviours and condom use
  – Must collect high-quality, extensive and reliable data on product and condom use

• Analysis adjusted for reported behaviours
  – Expected misclassification dilutes estimated effect

• Two control groups?
  – Costly, potentially confusing,
# HIV incidence in Active gel vs placebo vs no-product arm

<table>
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<tr>
<th>Scenario</th>
<th>Conclusion</th>
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<tbody>
<tr>
<td>Placebo = active = No-product (2%, 2%, 2%)</td>
<td>-Active not effective</td>
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<tr>
<td></td>
<td>-Placebo has no effect</td>
</tr>
<tr>
<td>Placebo &gt; active</td>
<td>-Active is effective?</td>
</tr>
<tr>
<td>No-product = active</td>
<td>-Placebo could be harmful</td>
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<tr>
<td>(3%, 2%, 2%)</td>
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<tr>
<td>Placebo = active</td>
<td>-Active is effective</td>
</tr>
<tr>
<td>No-product &gt; active</td>
<td>-placebo appears protective</td>
</tr>
<tr>
<td>(2%, 2%, 3%)</td>
<td>-ingredient in active is inactive</td>
</tr>
<tr>
<td>Placebo &gt; active</td>
<td>-Active is effective</td>
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Strength of Evidence

- Two independent studies at \( P < 0.05 \)
  - Desirable
  - Ethical Review Committees unlikely to approve
- Single study at \( P < 0.0013 \)
  - equivalent to two independent \( P < 0.05 \) studies
- Single \( P < 0.05 \) study may not convince
- When would a second study be no longer ethical? \( P < 0.05, 0.04, 0.03, 0.02, 0.01, \ldots \)?
Intermediate Trial Design

Phase 3 Trial Design

Further Studies

Positive

Courtesy: Thomas Fleming, PhD
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Rationale for Phase II Run-In

- “Traditional” Phase II studies - expanded safety and proof of concept
- No proven surrogates for either one at this time
- Sample sizes as large as for a Phase III
- HPTN 035 – 800 women will be followed under a phase II safety design with a DSMB review at the end of 3 months of follow-up
- Phase II participants contribute to the Phase III effectiveness analyses
- Study operations are maintained at the participating study sites throughout the Phase II/III transition
WHO Microbicide Project

• **Main objective**
  – To accelerate the development and deployment of a safe, effective and accessible topical microbicide for use especially in developing countries

• **Specific objectives**
  – To conduct clinical trials of promising candidate microbicides in countries with a major or emerging HIV epidemic
  – To develop and/or strengthen the research capacity of clinical sites in developing countries to participate in microbicide research
  – To facilitate discussions on ethics and derive an international consensus on the scientific basis for regulatory decisions on microbicides

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Research Capacity Strengthening for Microbicide Research

• Rationale:
  – many more microbicide leads going into human trials
  – few centers with experience on clinical trials in developing countries where microbicides are urgently needed
  – ensure the highest standards in the conduct of microbicide trials

• Selection of clinical sites interested in microbicide research

• needs assessment on research capacity

• capacity strengthening-staff training, facility upgrades, equipment, data management, networking

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Ethics and Regulatory Issues

• Facilitate discussions on ethics
  – ethical problems and challenges of microbicide research

• derive international consensus on prerequisites for microbicide research and registration
  – different views on competing requirements of urgency and proof of safety and effectiveness of microbicides
  – what safety and effectiveness data will national drug regulatory authorities need prior to registration of a microbicide in their country
  – Several international and regional meetings held in Switzerland, Botswana, India

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Acknowledgements

Colleagues in microbicide R&D committed to accelerating access to novel products

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